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Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence

Diffuse large B-cell lymphoma (DLBCL) constitutes 30%–58% of lymphoma series. The crude incidence in the European Union is 3–4/100 000/year. The incidence increases with age from 0.3/100 000/year (35–39 years) to 26.6/100 000/year (80–84 years) [1].

diagnosis

Diagnosis should be made on the basis of a surgical specimen/excisional lymph node or extranodal tissue biopsy providing enough material for formalin-fixed samples. Core biopsies may be appropriate as the only diagnostic test in the rare patients requiring emergency treatment. Minimal immunohistochemistry (CD45, CD20, and CD3) is mandatory. The collection of fresh frozen material for molecular characterization is recommended although gene expression profiling remains investigational. To ensure adequate quality, processing by an experienced pathology institute has to be guaranteed. The histological report should give the diagnosis according to the current World Health Organization classification [2].

The distinction between germinal center-like subtype and activated B-cell-like subtype, studied by gene expression profiling and suggested by immunohistochemistry, do not influence treatment choices at the moment [3].

staging and risk assessment

A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH) and uric acid as well as a screening test for human immunodeficiency virus and hepatitis B and C are required. Protein electrophoresis is recommended.

Patients amenable to curative therapy should have at least a computed tomography (CT) scan of the chest and abdomen, as well as a bone marrow aspirate and biopsy. A diagnostic spinal tap should be considered in high-risk patients [V, D].

[^{18}F]deoxyglucose positron emission tomography (PET) scanning is strongly recommended to better delineate the extent of the disease and in view to the evaluation of treatment response according to the revised criteria [4].

Performance status and cardiac function (left ventricular ejection fraction) should be assessed before treatment.

The staging is established according to the Ann Arbor system [I, A] (Table 1). For prognostic purposes, International Prognostic Index (IPI) and age-adjusted IPI (aa-IPI) should be calculated [I, A] [5].

treatment

Treatment strategies should be stratified according to age, age-adjusted IPI and feasibility of dose-intensified approaches (Table 2). Whenever available, the inclusion in a clinical trial should be considered.

In cases with high tumor load, precautions, as example by administering prednisone 100 mg p.o. several days as 'prephase' treatment, are required to avoid tumor lysis syndrome. Dose reductions due to hematological toxicity should be avoided. Febrile neutropenia justifies prophylactic use of hematopoietic growth factors in patients treated with curative intent and in all elderly patients.

young low-risk patients (aaIPI = 0) without bulky disease

Six cycles of combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment combined with six doses of rituximab given every 21 days is the current standard [I, A] [6]. Consolidation by radiotherapy to initial sites has proven no clear benefit [I, A] [7].

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young low-intermediate-risk patients (aaIPI = 1) or IPI low risk (aaIPI = 0) with bulky disease

R-CHOP 21 × 6 with radiotherapy to the sites of previous bulky disease was shown to be effective in this group of patients based on the results of the MINT study [6].

Table 1. Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localized involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
III	Involvement of lymphatic regions on both side of the diaphragm.
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement.

Alternatively, an intensification of chemotherapy with R-ACVBP (rituximab, doxorubicin, vindesine, cyclophosphamide, bleomycin, and prednisolone given every 2 weeks followed by sequential consolidation) has been shown to improve survival when compared with eight cycles of R-CHOP in this category, but in this trial, radiotherapy was omitted in both arms [I, A] [8]. In this group of patients either R-CHOP21 × 6 with radiotherapy to the sites of previous bulky disease or the intensified regimen R-ACVBP are recommended [II, B] [8, 9].

young high and high-intermediate-risk patients (aaIPI ≥ 2)

There is no current standard in this subgroup. Thus, especially this patient population should be treated preferably in clinical trials. Six to eight cycles of chemotherapy with CHOP combined with eight doses of rituximab given every 21 days are most frequently applied [III, B]. Dose-dense treatment with R-CHOP given every 14 days has not demonstrated survival

Table 2. Recommended treatment strategies in diffuse large B-cell lymphoma

Young <61 years		
IPI low risk no bulk	IPI low risk with bulk or IPI low-intermediate risk	IPI intermediate-high risk or IPI high risk
R-CHOP21 × 6 Consider CNS prophylaxis in patients at risk for CNS progression	R-ACVBP and sequential consolidation Or R-CHOP21 × 6 + IF-RT on bulk	R-CHOP21 × 8 or R-CHOP14 × 6 with 8 R Consider more intensive regimens: R-CHOEP14 × 6 or R-ACVBP plus HDCT with ASCT or R-dose-dense (R-CHOP14 like) plus R-HDCT with ASCT
Elderly >60 years		
Healthy	>80 years without cardiac dysfunction	UNFIT or FRAIL or >60 years with cardiac dysfunction
R-CHOP21 × 8 (R-CHOP21 × 6 for IPI low risk) or R-CHOP14 × 6 with 8 R Consider CNS prophylaxis in patients at risk	attenuated regimens: R-miniCHOP21 × 6	Doxorubicine substitution with etoposide or liposomal doxorubicine or others: R-C(X)OP21 × 6 or palliative care
First relapse/progress		
Eligible to transplant	Not eligible to transplant	
Platinum-based chemotherapy regimens (i.e. R-DHAP, R-ICE) as salvage treatment For chemosensitive patients: R-HDCT with ASCT as remission consolidation Consider allogeneic transplantation in patients relapsed after R-HDCT with ASCT or in patients with poor risk factors at relapse	Platinum and/or gemcitabine-based regimens Clinical trials with novel drugs	
>2 relapse/progress		
Eligible to transplant Allogeneic transplantation Clinical trials with novel drugs	Not eligible to transplant Clinical trials with novel drugs Palliative care	

advantage over standard R-CHOP given every 21 days [I, C] overall [10]. Moreover, in this trial, R-CHOP 14 failed to show a better outcome in each DLBCL subset, including young poor risk. The trial was however not powered enough to compare different clinical subgroups [10]. Intensive treatment with R-ACVBP or R-CHOEP is frequently used but these regimens have not been directly compared with R-CHOP in this category [II, B]. In the rituximab era, high-dose chemotherapy (HDC) with stem cell transplantation as consolidation treatment after immunochemotherapy has shown promising results in recent phase II trials [II, C] [11–13]. Recently, four randomized trials comparing R-HDC + ASCT versus R chemotherapy have been presented. Two trials show a PFS benefit for HDC with ASCT but no impact, at present, on survival [14, 15], while two trials failed to demonstrate an improvement for the HDC arm [16, 17]. Therefore, HDC with ASCT in first line remains experimental in first-line therapy or may be suggested for selective high-risk patients [II, C]. Consolidation by radiotherapy to sites of bulky disease has proven no benefit [III, C]. The role of radiotherapy in partial remission remains to be established in patients treated with rituximab and evaluated with PET [18].

patients aged 60–80 years

Eight cycles of combination chemotherapy with CHOP treatment combined with eight doses of rituximab given every 21 days is the current standard [I, A] [19]. R-CHOP given every 14 days did not demonstrate survival advantage over R-CHOP 21 [I, C] [10, 20]. If rituximab-CHOP is given every 14 days, six cycles of CHOP with eight cycles of rituximab are sufficient [21]. In patients with localized disease, consolidation by radiotherapy has proven no benefit [I, A] [22] in patients treated prior the introduction of rituximab.

patients aged >80 years

A comprehensive geriatric assessment is recommended to help determine choice of treatment in these patients. R-CHOP treatment could usually be used until 80 years of age in healthy patients. The combination of rituximab with attenuated chemotherapy, as R-miniCHOP, could induce complete remission and long survival in healthy patients older than 80 years [III, B] [23]. The doxorubicin substitution with etoposide or liposomal doxorubicin or even its omission can be considered from the beginning or after a few cycles in patients with cardiac dysfunction or otherwise unfit [IV, C].

CNS prophylaxis

Patients with high-intermediate and high-risk IPI, especially those with more than one extranodal site or elevated LDH are at higher risk of central nervous system (CNS) relapse [24]. CNS prophylaxis should be recommended in this population but intrathecal injections of methotrexate are probably not an optimal method. Intravenous high-dose methotrexate associated with efficient disease control could be an interesting alternative [IV, C] [25, 26]. Whether some specific involvement sites as paranasal sinus, upper neck or bone marrow should receive prophylaxis remains to be established [27]. Testicular lymphoma must receive CNS prophylaxis.

some extranodal DLBCL require special consideration

Treatment of primary DLBCL of the central nervous system must contain high-dose methotrexate. Addition of high-dose cytarabine seems to improve complete remission rate and outcome [28]. CNS irradiation is usually administered as consolidation.

Primary DLBCL of the testis (PTL) is characterized by an increased risk of extranodal, CNS, and contralateral testis recurrence with poor outcome [29]. The standard treatment of localized (stage I to II) PTL is R-CHOP21 with CNS prophylaxis and contralateral testis irradiation [III, A] [30]. An open issue remains the type of CNS prophylaxis either with intrathecal chemotherapy or with the addition of intravenous high-dose methotrexate or both.

Primary mediastinal large B-cell lymphoma is probably a distinct entity. R-CHOP 21 is not established as the definitive treatment option and radiotherapy remains controversial [31].

response evaluation

Abnormal radiological tests at baseline should be repeated after three to four cycles and after the last cycle of treatment. Bone marrow aspirate and biopsy should be only repeated at the end of treatment if initially involved [4].

PET is highly recommended for the post-treatment assessment to define complete remission according to the revised criteria of response [4]. In case of therapeutic consequences, a histological confirmation of PET positivity at this time is strongly recommended. Early PET, performed after one to four cycles of treatment, have been shown to be predictive of clinical outcome in some studies, but others did not find any correlations and its results should not lead to treatment change outside of a clinical trial.

follow-up

History and physical examination every 3 months for 1 year, every 6 months for 2 more years, and then once a year with attention to development of secondary tumors or other long-term side-effects of chemotherapy [V, D].

Blood count and LDH at 3, 6, 12, and 24 months, then only as needed for evaluation of suspicious symptoms or clinical findings in those patients suitable for further therapy [V, C].

Minimal adequate radiological examinations at 6, 12, and 24 months after end of treatment by CT scan are usual practice, but there is no definitive evidence that routine imaging in patients in complete remission provides any outcome advantage [27, 32]. Routine surveillance with PET scan is not recommended. High-risk patients with curative options may potentially mandate more frequent controls.

relapsed and refractory DLBCL

incidence

Overall, >30% of DLBCL will ultimately relapse. The incidence in the European Union is therefore estimated to be around 1/100 000/year.

diagnosis

Histological verification should be obtained whenever possible, and is mandatory in relapses >12 months after the initial diagnosis, especially in order to ensure CD20 positivity. Image-guided core biopsy may be appropriate in this context.

staging and risk assessment

Patients still amenable to curative therapy should have the same examinations as at first diagnosis.

treatment

The following recommendations apply to patients with adequate, rituximab-associated anthracycline-containing first-line therapy.

In suitable patients with adequate performance status (no major organ dysfunction, age <65–70 years), salvage regimen with association of rituximab and chemotherapy followed in responsive patients by high-dose treatment with stem-cell support is recommended [II, A] [33, 34]. Salvage regimens such as R-DHAP (rituximab, cisplatin, cytosine arabinoside, and dexamethasone) or R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) did not exhibit different outcome [35]. The possible advantage of R-DHAP in the germinal center B-cell-like subtype must be confirmed [36]. BEAM (carmustine, etoposide, cytosine-arabinoside, and melphalan) is the more frequently used high-dose regimen. Additional involved-field radiation or iceberg radiation may be used especially in the few cases with limited stage disease, but it has been never evaluated in controlled trials. Maintenance with rituximab in responding patients is not recommended [I, D] [37]. Allogeneic transplantation following chemotherapy should probably be considered in patients with refractory disease, early relapse or relapse after ASCT [III, B] [38].

Patients not suitable for high-dose therapy may be treated with the same or other salvage regimens as R-GEMOX (rituximab, gemcitabine, and oxaliplatin), which may be combined with involved-field radiotherapy [39] or preferentially be enrolled in clinical trials testing the activity of novel drugs.

response evaluation

Response criteria are identical to those of first-line treatment evaluation [4]. An evaluation should be performed after three to four cycles of salvage regimen (before high-dose treatment) and after the end of all therapy. The results of PET before high-dose treatment are correlated to clinical outcome.

follow-up

Follow-up of patients in second response could be the same as first response.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

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